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(54) Title: STABLE LIPOSOMES OR MICELLES COMPRISING A SPHINOLIPID AND A PEG-LIPOPOLYMER

(57) Abstract: The present invention concerns a stable lipid assembly comprising a biologically active lipid having a hydrophobic region and a polar headgroup, wherein the atomic mass ratio between the headgroup and hydrophobic region is less than 0.3, and a lipopolymer having a hydrophobic lipid region and a polymer headgroup, wherein the atomic mass ratio between the headgroup and hydrophobic region is at least 1.5 and optionally a lipid matrix composed of liposome forming lipids. Specific lipid assemblies according to the invention comprise the biologically active lipid, ceramide, a lipid derivatized with polyethylene glycol (lipopolymer) and optionally in combination with a phospholipid (e.g. Egg phosphatidylcholine (EPC) and hydrogenated soybean phosphatidylcholine (HSPC)). The lipid assemblies of the invention exhibited a therapeutic effect in vitro in tumor cells as well as in vivo in animal models and they deliver the biologically active lipid to the disease site.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/127 A61K9/107 A61K31/164

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/000227 A (BARENHOLZ YECHEZKEL ; YISSUM RES DEV CO (IL); KEDAR ELIEZER (IL)) 3 January 2003 (2003-01-03) page 12, line 11 - line 28; claims 3,9,10	1-80
X	WO 03/000232 A (BARENHOLZ YECHEZKEL ; YISSUM RES DEV CO (IL); KEDAR ELIEZER (IL); JOSE) 3 January 2003 (2003-01-03) claims 3,9,10	1-80
X	WO 94/07466 A (LIPOSOME TECHNOLOGY INC) 14 April 1994 (1994-04-14) example 6; table 5 example 7; table 6	1-80
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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Date of the actual completion of the international search

23 November 2004

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06/12/2004

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ALLEN T M ET AL: "LIPOSOMES CONTAINING SYNTHETIC LIPID DERIVATIVES OF POLY(ETHYLENE GLYCOL) SHOW PROLONGED CIRCULATION HALF-LIVES IN VIVO" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, vol. 1066, 1991, pages 29-36, XP000672933 ISSN: 0006-3002 tables I,II	1-80
X	WEBB M S ET AL: "COMPARISON OF DIFFERENT HYDROPHOBIC ANCHORS CONJUGATED TO POLY(ETHYLENE GLYCOL): EFFECTS ON THE PHARMACOKINETICS OF LIPOSOMAL VINCRISTINE" BIOCHIMICA ET BIOPHYSICA ACTA, AMSTERDAM, NL, vol. 1372, 1998, pages 272-282, XP000964651 ISSN: 0006-3002 table I	1-80
X	US 6 287 591 B1 (CULLIS PIETER ET AL) 11 September 2001 (2001-09-11) column 28, line 33 - line 51; example 4 example 7; table 2	1-80
X	US 5 885 613 A (HOLLAND JOHN W ET AL) 23 March 1999 (1999-03-23)	1-80
Y	column 7, line 55 - line 63 column 8, line 34 - column 9, line 5 claim 1	1-80
Y	SIMON, C.G. ET AL.: "Exchange of C16-ceramide between phospholipid vesicles" BIOCHEMISTRY, vol. 38, 1999, pages 14676-14682, XP002307118 See "Materials and Methods" page 14677, left-hand column	1-80
Y	BAI, J. ET AL.: "Measurement of spontaneous transfer and transbilayer movement of BODIPY-labeled lipids in lipid vesicles" BIOCHEMISTRY, vol. 36, 1997, pages 8840-8848, XP002307119 See "Materials and Methods" page 8841, right-hand column	1-80
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>RUIZ-ARGÜELLO, M.B., ET AL.: "Different effects of enzyme-generated ceramides and diacylglycerols in phospholipid membrane fusion and leakage" THE JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 43, 25 October 1996 (1996-10-25), pages 26616-26621, XP002307120 See "Materials and Methods" page 26616, right-hand column -----</p>	1-80
P,X	<p>STOVER, T. ET AL.: "Liposomal delivery enhances short-chain ceramide-induced apoptosis of breast cancer cells" THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 307, no. 2, November 2003 (2003-11), XP002307125 page 472, left-hand column -----</p>	1-80

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2004/000294

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 54-80 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-80 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 54-80 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

Continuation of Box II.2

Claims Nos.: 1-80 (in part)

Present independent claim 1 relates to an extremely large number of possible "lipid assemblies", namely any combination comprising a "biologically active lipid" and a "lipopolymer", both components being defined only in terms of a parameter, namely the "atomic mass ratio between the headgroup and the hydrophobic region". Claims 2, 3 and 4 contain further parametric definitions ("additive packing parameter" and "level of water tightly bound to said lipopolymer headgroup"). The claims cover all possible combinations of a "biologically active lipid" and a "lipopolymer" having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a limited number of such combinations, namely liposomes or micelles comprising: 1) a sphingolipid ("biologically active lipid"), 2) a pegylated lipid ("lipopolymer"), and 3) a phospholipid, in the sense of claims 1, 5, 11, 14, 21 and 22 taken in combination, and as interpreted in connection with the description and the examples. The application only provides disclosure and/or support for the combination of components 1), 2) and 3) as defined above. The area covered by claim 1 is broader than justified by the extent of the disclosure. In the present case, claim 1 so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. It is the same for independent claims 26 and 54.

Furthermore, the use of the aforementioned parametric definitions in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the subject-matter as defined above.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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